

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Cuttitta *et al.*

Application No. 10/571,012

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For: NON-PEPTIDE ANTAGONISTS OF
GASTRIN RELEASING PEPTIDE

Examiner: Anna Pagonakis

Art Unit: 1628

Attorney Reference No. 4239-82094-06

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DECLARATION OF DR. JAMES L MULSHINE UNDER 37 C.F.R. § 1.132

I, James L Mulshine M.D. declare as follows:

1. I have read and am familiar with U.S. Patent Application No. 10/571,012 (hereinafter, "the subject application").
2. I hold a MD with board certification in Internal Medicine and Medical Oncology and completed a post-doctoral fellowship in lung cancer tumor biology at the NCI. My *curriculum vitae* is submitted herewith as Exhibit GG. By virtue of my education, training, and professional experience, I am knowledgeable about the biology of cancer, angiogenesis, and gastrin releasing peptide (GRP).
3. I have read the Office Action dated May 26, 2011 and the references cited therein.
4. I understand that the Office asserts that the claims of the subject application are allegedly anticipated by Japanese Patent No. 10212235 (hereafter JP10212235) as evidenced by the National Cancer Institute Slide entitled "What is tumor angiogenesis?" (hereinafter the NCI Slide), and as evidenced by Patel *et al* (*Biochim et Biophys Acta*, 1766:23-41, 2006).

5. Anti-tumor activity is not necessarily an anti-GRP activity

5.1. The Office asserts that JP10212235 inherently describes an anti-GRP activity because it describes Compound I as an anti-tumor compound, and because Patel *et al.* teaches that GRP and/or the GRP receptor is expressed in many tumor types that are also listed in JP10212235. Based on my training and experience in cancer biology, I do not think that this generalization is possible without supporting data, which JP10212235 does not provide.

5.2 The transformation of a normal cell into a cancerous cell involves the possible perturbation of myriad cellular pathways. The development of a cancerous cell into a tumor and the progression of that tumor into a life-threatening disease are equally complex. Thus, in describing generic Compound I as an “anti-tumor compound” JP10212235 is potentially describing hundreds of possible biological activities. Moreover, even within the same tumor type, there are frequently subpopulations of cells that possess disparate biological characteristics. Notwithstanding the listing in Patel *et al.* of tumor types that express GRP and/or the GRP receptor, there will exist populations of cells in these tumors that do not express these proteins. Thus, GRP and/or the GRP receptor will not necessarily be expressed in the tumors listed in JP10212235.

5.3. The principle that a characteristic may be present in one cell population of a tumor type, but absent in another cell population of the same tumor type is illustrated by Moody *et al.* (*J. Cell. Biochem. Supp.*, 24:247-256, 1996; submitted with the Request for Continued Examination of April 28, 2011 as Exhibit AA). Moody *et al.* assay for the presence of the GRP receptor in several small cell lung cancer cell lines and several non-small cell lung cancer cell lines. Moody *et al.* observed that the GRP receptor is abundantly present in many, but not all of the cell lines tested. Table I of Moody *et al.* shows that only 42% of small cell lung cancer and 32% of non-small cell cancer cell lines tested express the GRP receptor at levels of any biological significance. Thus, an aberrant GRP activity would affect less than half of the cell lines tested, and a treatment targeting that activity would only be effective 42% and 32% of the time, respectively.

5.4. Because of the multiple levels of complexity associated with tumor development, it would be incorrect to assume that all cancer patients are suffering from an aberrant activity of gastrin releasing peptide, and one of skill would not assume anything about the properties of a tumor or tumor treatment in the absence of experimental evidence that characterizes the tumor or treatment. JP10212235 provides no data that would allow one of skill to identify the biological activity that is targeted by Compound I, and does not imply that an aberrant GRP activity is being targeted. JP10212235 supports its assertion that Compound I is effective by two experimental assays, but neither of the assays identified a molecular target for Compound I. In the first assay, a subset of nine species of Compound I (Compounds 14, 44, 45, 63, 64, 70, 71, 78, and 125) were tested for the ability to inhibit proliferation of 54 cancer cell lines. Although many of the tested compounds inhibited proliferation, JP10212235 does not present data for all of the compounds (see for example Table 30). In the second assay of the “anti-tumor” effect, Compound 44 was administered to a mouse that was injected with a leukemia cell line. The length of time that the mouse survived in the presence or absence of the Compound was then compared. No assay as to the *in vivo* effect of Compound 44 on the leukemia was performed.

5.5 In contrast to the relatively uncharacterized effect described in JP10212235, the pending claims are directed to specific inhibition of an aberrant activity of GRP by a small molecule mimetic of a GRP neutralizing antibody (Compound 77427, referred to as Compound XV' in the claims). Compound 77427 is able to compete with MoAb 2A11 for specific binding to GRP (see specification, at page 17, lines 10-16, and Table 1, pages 18-19). As with any specific molecular interaction, the ability for Compound 77427 to bind to GRP results from its shape and charge. Just as changes to an antibody structure will change its binding specificity, so too changes to a small molecule compound (such as Compound 77427) will also change its binding specificity, and by extension biological activity. Therefore, without demonstrating that Compound I and its species share the ability to bind to and inhibit GRP, I would not assume that Compound I will necessarily bind and inhibit GRP, just because GRP is a known tumor promoting factor.

5.6. JP10212235 lists Compound 105 as a species of Compound I. Compound 105 is the same as claimed Compound 77427, but apart from being listed as a species of Compound I,

Compound 105 is not further described in JP10212235. It is not among the nine compounds tested for anti-proliferation activity, and it is not the used in the *in vivo* survival assay of a mouse injected with leukemia. Previously, the Office was provided with a composite list of the Compounds that were used in the experiments of JP10212235, in comparison to Compound 105 (submitted with the Request for Continued Examination on April 28, 2011 as Exhibit DD). As presented in Exhibit DD, the nine compounds tested by JP10212235 have a striking similarity: a large cyclic functional group at position R3. This large functional group is entirely absent from Compound 105. Because of this substantial difference in structure, and notwithstanding any activity shared by Compounds 14, 44, 45, 63, 64, 70, 71, 78, and 125, I would not expect Compound 105 to share the same specific activity with these compounds. Likewise, I would not expect the tested compounds to share the same specific activity as Compound 105. Moreover, because of the substantial differences in chemical structure between all of the 131 species of Compound I, I would not expect there to be any necessarily shared characteristic of all of the species of Compound I without supporting data of such a shared characteristic.

5.7. I understand that Dr. Cuttitta has tested a species of Compound I, Compound 109 (NSC 619198) and which is structurally similar to Compound 77427, for the ability to block the binding of MoAb2A11 to GRP. I have reviewed this data, which is provided herewith as Exhibit EE. I have also reviewed Dr. Cuttitta's Declaration, in which he describes the experiments and data shown in Exhibit EE. I concur with Dr. Cuttitta's interpretation that the data shown in Exhibit EE demonstrates that Compound 109 does not significantly block the ability for MoAb2A11 to bind to GRP. This data not only confirms the assumption that experimental evidence is necessary to prove that a class of compounds share the same specific activity, but it also supports the conclusion that the "anti-tumor activity" of described by JP10212235 is not an anti-GRP activity necessarily shared by Compound I and all of its species..

6. The patient populations in JP10212235 and Patel *et al.* are not the same

6.1. As discussed above, myriad biological activities may be implicated in the transformation of a normal cell to a cancerous cell. It is for this reason that not every cancer type

is susceptible to the same treatment. Additionally as discussed above, even within the same tumor type, biological variability exists.

6.2. The Office asserts that Patel *et al.* evidences that, by describing an anti-tumor activity, JP10212235 is inherently describing an ant-GRP activity. This is not so. Patel *et al.* describes GRP as an agent implicated in many cancers, and describes the cell types known to express GRP and the GRP receptor. But Patel *et al.* does not describe all of the tumor types listed by JP10212235. In particular Patel *et al.* does not describe leukemia as expressing GRP and/or the GRP receptor. Indeed, it is known that GRP is not implicated in development and progression of leukemia. In contrast, JP10212235 describes leukemia as a tumor type that may be treated using Compound I and its species. By indicating that Compound I and its species are effective against a group of cancers that includes leukemia, JP10212235 implies that a biological activity other than an aberrant GRP activity is targeted by Compound I. Thus, contrary to the Office's assertion, Patel *et al.* proves that JP10212235 is not teaching inhibition of a GRP activity. Similarly, because the group of tumors described by JP10212235 includes leukemia, the described tumor types, and consequently described patient population, is not the same as that described by Patel *et al.* This is because a group of patients that includes patients with a non-GRP-associated tumor have not been "selected" for having an aberrant GRP activity. Thus, Patel *et al.* also proves that JP10212235 does not inherently contain a step of selecting for a patient who is aberrantly expressing GRP.

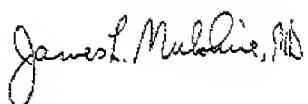
7. Anti-tumor activity is not necessarily anti-angiogenesis activity

7.1. The Office indicates that "treatment of a tumor would necessarily inhibit angiogenesis since angiogenesis is responsible for progression of the disease" (Office action, at page 4). As discussed above, development and progression of a tumor is the combination of myriad biological processes. Angiogenesis is only one category of processes necessary for tumor development and progression. In addition to angiogenesis, a cancer cell must be able to proliferate. The NCI slide provides no evidence to the contrary. The NCI slide merely illustrates that tumors are able to induce angiogenesis to facilitate tumor growth. The NCI slide makes no statement that all anti-tumor treatments must necessarily inhibit angiogenesis. A cancer cell may

secrete factors to stimulate robust angiogenesis, but if the cancer cell is unable to proliferate uncontrollably it will not develop into a tumor and will not progress into a life-threatening disease. Thus, a given anti-tumor therapy might target angiogenesis, but it might alternatively target cellular proliferation. While treatments exist that target both proliferation and angiogenesis, many treatments target these processes individually. This variety of anti-tumor targets is well known and is illustrated by the list of treatments with varying targets in the table on page 118 of Butowski and Chang, *Cancer Control*, 12:116-124, 2005, which was submitted with the Request for Continued Examination on April 28, 2011 as Exhibit CC. I note that while Butowski and Chang discuss the importance of angiogenesis in glioma development, not all of the potential therapies discussed therein target angiogenesis.

7.2. Because different anti-tumor treatments can target different processes, I would not assume any particular target for a given “anti-tumor treatment.” JP10212235 does not state that Compound I and its species can be used to inhibit angiogenesis. Nor does JP10212235 describe any experiments that use Compound I as an anti-angiogenic agent. Indeed, the only anti-tumor activity indicated by JP10212235 is an anti-proliferative activity.

8. I hereby declare that all statements made herein are of my own knowledge, are true and that all statements made on information and belief are believed to be true. Furthermore, these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



10/26/2011 _____
Date Name James L Mulshine, M.D.